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(54) Title: TREATMENT OF CONGESTIVE HEART FAILURE WITH GROWTH HORMONE SECRETAGOGUES

(57) Abstract

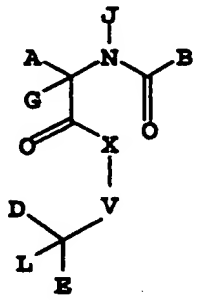
The invention provides methods for the modulation of cardiac function by the administration of a growth hormone secretagogue, wichch results in an increase in the levels of endogenous growth hormone. Also provided are methods for the treatment of congestive heart failure by the administration of a growth hormone secretagogue. Further provided are methods for the treatment of congestive heart failure by the administration of a growth hormone secretagogue in combination with a growth hormone releasing hormone, or in combination with an antihypertensive agent, diuretic, or other suitable agents.

We Claim:

1. A method of modulating cardiac function which comprises administering to a patient in need thereof an effective amount of a growth hormone secretagogue.

2. A method according to Claim 1 wherein said growth hormone secretagogue comprises GRP-2.

3. A method according to Claim 1 wherein said growth hormone secretagogue comprises a compound of formula I



I

wherein:

A is C_1-C_6alkyl, aryl, C_1-C_6alkylaryl, C_1-C_6alkyl(O)C_1-C_6alkylaryl, C_1-C_6alkyl(S)C_1-C_6alkylaryl, indolyl, indolinyl, thienyl, (C_1-C_6alkyl)thienyl, benzothienyl, benzofuranyl, naphthanyl, cyclohexyl, (C_1-C_6alkyl)indolyl, (C_1-C_6alkyl)benzothienyl, (C_1-C_6alkyl)naphthanyl, (C_1-C_6alkyl)benzofuranyl, and (C_1-C_6alkyl)cyclohexyl;

B is NH_2, NHR_1, C_1-C_6alkylNH_2, C_1-C_6alkylNHR_1, C_1-C_6alkylarylNH_2, C_1-C_6alkylarylNHR_1,

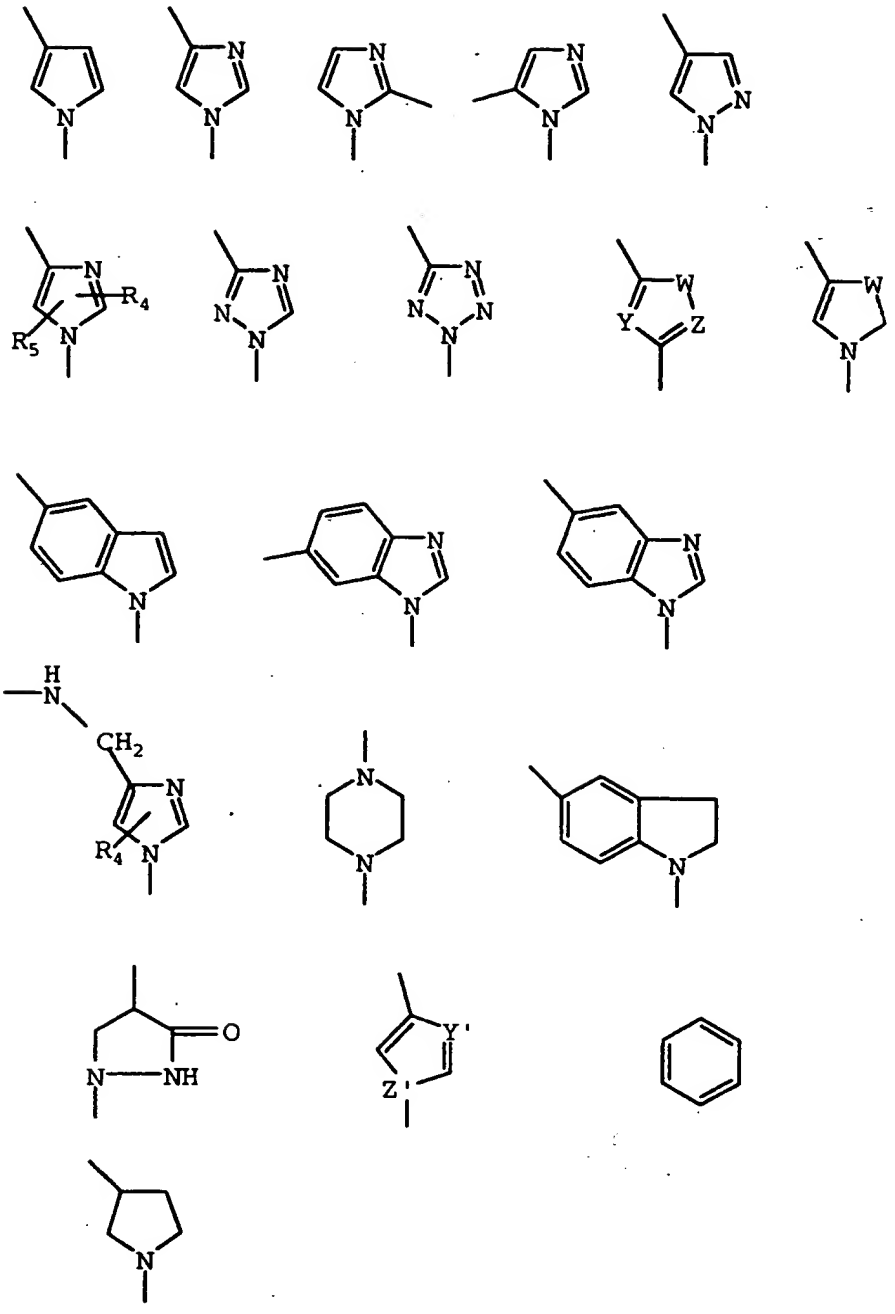
C_1-C_6alkylcyclohexylNH_2, C_1-C_6alkylcyclohexylNHR_1,
R_1-piperidin-3-yl(C_1-C_6alkyl),
R_1-piperidin-2-yl(C_1-C_6alkyl), R_1-piperidin-4-yl(C_1-C_6alkyl),
R_1-quinolin-2-yl(C_1-C_6alkyl),
R_1-(2,4-dihydroquinolin-2-yl(C_1-C_6alkyl),
R_1-isoquinolin-2-yl(C_1-C_6alkyl), and
R_1-(2,4-dihydroisoquinolin-2-yl(C_1-C_6alkyl);

R_1 is hydrogen, C_1-C_6alkyl, C_1-C_6alkyl(OH), or C_1-C_6alkylidenyl(OH)R_2;

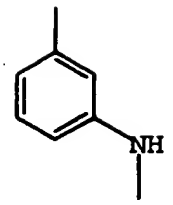
R_2 is C_1-C_6alkyl, C_1-C_6alkenyl, C_1-C_6alkyl(O)C_1-C_6 alkyl, C(O)O-C_1-C_6 alkyl, aryl, or C_1-C_6alkylaryl;

X is C_1-C_6alkylidenyl, O, S, NH, or N(C_1-C_6alkyl);

V is selected from the group consisting of



and



;

W is S, O, NH, or CH_2;

Y is N or CH;

Z is N or CH;

Y' is N or CH;

Z' is N or CH;

R_4 and R_5 are independently hydrogen, C_1-C_6alkyl, aryl, C_1-C_6alkylaryl, C(O)O(C_1-C_6alkyl), C(O)N(C_1-C_6alkyl)$_2$, or C_1-C_6alkylCOR_7;

R_7 is hydrogen, C_1-C_6alkyl, pyrrolidinyl, piperidinyl, homoproline, or proline;

D is hydrogen, C_1-C_6alkyl, C_1-C_6alkyl(O)(CO)C_1-C_6alkyl, C_1-C_6alkyl(O)(CO)N(C_1-C_6alkyl)$_2$, C_1-C_6alkylaryl, C(O)R_6, C_1-C_6alkyl(O)R_6, C_1-C_6alkyl(OH), C_1-C_6 alkylC(O)R_6, C_1-C_6alkylR_6, aryl, (C_1-C_6alkyl)$NHSO_2$(C_1-C_6alkyl), (C_1-C_6alkyl)$NHSO_2$(aryl);

R_6 is H, C_1-C_6alkyl, aryl, naphthyl, C_1-C_6alkylaryl, acetyl, NH_2, NH(C_1-C_6alkyl), NH(C_1-C_6alkyl)O(C_1-C_6alkyl), NH(C_1-C_6alkyl)S(C_1-C_6alkyl), NH(C_1-C_6alkylidenyl)OCH_3, NH(C_1-C_6alkyl)aryl, NH(C_3-C_6 cycloalkyl), NH(C_1-C_6alkyl)C(O)(C_1-C_6alkyl), NH(C_1-C_6alkyl)NH(C_1-C_6alkyl), NH(C_1-C_6alkyl)NH(C_1-C_6alkylaryl), $NHSO_2$(C_1-C_6alkylaryl), NH(C_1-C_6alkyl)C(O)O(C_1-C_6alkyl), NH(naphthyl),N(C_1-C_6alkyl)$_2$, N(C_1-C_6alkyl)(aryl), N(C_1-C_6alkyl)(C_1-C_6alkylaryl), O(C_1-C_6alkyl), O(aryl), O(C_1-C_6alkylaryl), piperidinyl, piperidinyl-C(O)NH(C_1-C_6alkyl), piperidinyl-C(O)NH(C_1-C_6alkylaryl), piperidinyl-C(O)N(C_1-C_6alkyl)$_2$, piperidinyl-C(O)N(C_1-C_6alkyl)(aryl), pyrrolidinyl, pyrrolidinyl C(O)NH(aryl),

pyrrolidinyl C(O)NH(C_1-C_6alkyl),
pyrrolidinyl C(O)N(C_1-C_6alkyl)$_2$,
pyrrolidinyl C(O)NH(C_1-C_6alkylaryl),
pyrrolidinyl C(O)NH(C_1-C_6alkyl)(aryl),
pyrrolinyl, morpholino, hexamethyleneimino, heptamethyleneimino, quinolinyl, 2,4-dihydroquinolinyl, 1,2,3,4-tetrahydroquinolinyl, 2,4-dihydroisoquinolinyl, 1,2,3,4-tetrahydroisoquinolinyl, indolinyl, an amino acid selected from the group consisting of proline, homoproline, glycine, alanine, valine, leucine, isoleucine, tyrosine, tryptophan, phenylalanine, serine, threonine, asparagine, glutamic acid, aspartic acid, lysine, arginine, glutamine, histidine, cysteine, and methionine, or a nitrogen-containing heterocycle selected from the group consisting of